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EXAMINER	
KINSEY, NICOLE	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,340	BERZOFSKY ET AL.	
	Examiner	Art Unit	
	Nicole E. Kinsey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-42 and 44-69* is/are pending in the application.

4a) Of the above claim(s) *17-20, 24, 38-41, 45-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,21,23,25-37,42 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election with traverse of Group I (claims 1-16, 21, 23, 25-37, 42 and 44) filed on March 6, 2007 is acknowledged. The traversal is on the grounds that i) PCT Lack of Unity Rules should apply to a divisional of an application filed under 35 U.S.C. § 371, ii) all groups relate to a shared technical feature, and iii) dependent claims share unity if the claims from which they depend share unity. These arguments are not found persuasive for the following reasons.

With regard to traversal (i), when the Office considers international applications as an International Searching Authority, as an International Preliminary Examining Authority, and during the national stage as a Designated or Elected Office under 35 U.S.C. 371, PCT Rule 13.1 and 13.2 will be followed when considering unity of invention of claims of different categories without regard to the practice in national applications filed under 35 U.S.C. 111. No change was made in restriction practice in United States national applications filed under 35 U.S.C. 111 outside the PCT (see MPEP § 1850 (I)). Therefore, it is improper to use PCT Lack of Unity Rules with U.S. applications filled under 35 U.S.C. 111 using the procedures set forth in 37 CFR 1.53(b). With regard to traversal ii), the Requirement for Restriction (Lack of Unity) mailed on October 10, 2006 was based on the claims that were pending at that time, not the currently amended claims. As for traversal iii), the independent claims that were pending in October did not and still do not share a common technical feature, and therefore, lack unity. Further, each polypeptide sequence recited in groups I-XVIII is

distinct from the other because each sequence is structurally different and has a different function. A search for one sequence will not be commensurate in scope with a search for any other sequence. Each sequence has different amino acid content and varying lengths. A search for each sequence would be a serious search burden on the PTO resources since each sequence requires a separate search performed in the patent and non-patent literature databases.

Thus, the requirement is still deemed proper and is therefore made **FINAL**.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Appropriate correction is required.

Applicants are required to update the first paragraph of the specification to provide the correct status (i.e., "abandoned" or "now Patent No. 1,234,567") of each application, if necessary. Appropriate correction is required.

Claim Objections

Claims 4, 7 and 12 are objected to because of the following informalities: Claims 4, 7, and 12 recite improper Markush language (i.e., "or" instead of "and"). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 21, 23, 25-37, 42 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

Nature of the invention. The instant invention is drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising any purified soluble antigen, including HIV. The phrase "inducing a protective rectal mucosal CTL response" indicates a vaccine. The term "vaccine," by definition, implies a preparation intended for active immunological prophylaxis. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease.

State of the prior art. It is well known in the art and even to the general public that medical science, despite decades of intense research, has not found any antigen, immunogen, or compound that can be credibly used as a vaccine against HIV.

The difficulties inherent to developing an HIV vaccine are well known. For the sake, of clarity, some of those problems are outlined here:

1) the extensive genomic diversity associated with HIV, due in large part to error prone reverse transcription of its RNA genome,

2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert form (cell to cell transmission), as well as via free virus transmission,

3) the existence of latent forms of the virus,

4) the complexity and variation of the elaboration of the disease, and

5) the property of some portions of HIV proteins or peptides to actually cause immunosuppression or other detrimental consequences.

The existence of these obstacles prevents one of ordinary skill in the art from accepting any therapeutic regimen on its face given the intense interest in developing HIV treatments or vaccines and the lack of success in doing so.

Working examples. The specification contains examples showing the vaccination of mice and the induction of antigen-specific CTLs. None of the examples, however, show rectal mucosal vaccination and challenge with HIV resulting in complete protection or prevention of HIV infection.

Guidance in the specification. The claimed invention is directed to a rectal mucosal vaccine against HIV. There is insufficient disclosure to reasonably predict that the claimed vaccine of the instant specification would prevent HIV infection. In addition, the disclosure fails to provide any guidance pertaining to the correlates of human

protection. To date, it is not clear what type of immune response is required to provide a therapeutic benefit.

The disclosure also fails to provide any guidance pertaining to the development of a persistent and protective HIV-1-specific immune response. It is not readily apparent if the recited HIV vaccine will generate an HIV-1-specific immune response of sufficient magnitude and duration that long-lasting protection against HIV-1 infection and the development of AIDS would be provided.

Applicants have shown immunogenicity studies in mice and mucosal challenge studies with vaccinia virus expressing HIV gp160 studies. While the specification does contain statements regarding the use of peptides as an HIV vaccine, there is no indication that an HIV-1-specific immune response has been generated and that such a response, if generated, would be protective following exposure to HIV-1. Applicants have not provided any evidence in the instant specification that the disclosed immunogens can prevent HIV infection or HIV-1 transmission following the administration of said vaccine.

Predictability or unpredictability of the art. The state-of-the-art vis-a-vis HIV vaccine development is one of unpredictability (Haynes et al., 1996; Burton and Moore, 1998; Moore and Burton, 1999; Desrosiers, R., 2004). To date, there is not one single effective HIV vaccine on the market. Several clinical trials have been conducted but in every situation, the immunogen failed to induce a long-lasting and high-titer immune response.

Accordingly, when all the aforementioned factors are considered *in toto*, it would require undue experimentation for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 6 and 27 recite the limitation "the cytokine" in reference to claims 1 and 25, respectively. There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4 and 15 are rejected under 35 U.S.C. § 102(a) as being anticipated by Klavinskis et al. (Journal of Immunology, 1996, 157: 2521-2527).

The claims are drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising a purified soluble antigen.

Klavinskis et al. teaches rectal and vaginal immunization by administering an SIV peptide covalently linked to cholera toxin B subunit (CTB). CTB was used as an

adjuvant, which is "essential to elicit a mucosal immune response." See page 2522 – Immunization schedule. Klavinskis et al. showed that that CTLs were isolated from the rectal mucosa and antigen-specific (see page 2524).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klavinskis et al. in view of Kiyono et al. (Advanced Drug Delivery Reviews, 18: 23-51) and Ahlers et al. (The journal of Immunology, 158: 3947-3958).

The claims are drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a

rectal mucosal tissue of the subject with a composition comprising a purified soluble antigen, wherein the method further comprises administering a purified cytokine, e.g., GM-CSF, IL-2, IL-7, IL-12, IFN-γ or TNF-α, to the subject.

The teachings of Klavinskis et al. are outlined above. Klavinskis et al. does not teach administering a cytokine to the subject. However, Ahlers et al. teaches immunizing a subject with the peptide of SEQ ID NO:9 and various cytokines (GM-CSF, IL-2, IL-12, IFN-γ or TNF-α). Ahlers et al. found that GM-CSF synergized with IL-12 for CTL induction. TNF-α also synergized with IL-12, but by a different mechanism, inducing IFN-γ production, thus shifting the response to a Th1 phenotype (see abstract). Ahlers et al. suggests that in addition to IL-2, optimum induction of CD8+ CTL *in vivo* requires a combination of cytokines, including GM-CSF and IL-12 (steering the Th response toward Th1 cytokines) (see the abstract and the Results section on page 3949).

It would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis et al. to also administer cytokines to the subject. One would have been motivated to do so given the suggestion by Kiyono et al. that Th cell-derived cytokines are essential for the induction of appropriate antigen-specific mucosal immune responses (see bottom of page 23) and the teachings of Ahlers et al. There would have been a reasonable expectation of success given the findings of Ahlers et al. with regard to CTL induction by cytokines. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 16, 21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klavinskis et al. and either Ahlers et al. or Berzofsky et al. (WO 94/26785).

The claims are drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising a purified soluble antigen, wherein the antigen is the peptide of SEQ ID NO:9 derived from HIV-1.

The teachings of Klavinskis et al. are outlined above. Klavinskis et al. does not teach SEQ ID NO:9 or an antigen from HIV-1. However, both Ahlers et al. and Berzofsky et al. disclose the peptide of SEQ ID NO:9 (see page 3948 of Ahlers et al. and SEQ ID NO:28 and claim 15 of Berzofsky et al.). Both references describe the peptide of SEQ ID NO:9 as being derived from HIV-1, as an inducer of cytotoxic T cells, and useful for therapeutic or prophylactic vaccines against HIV.

It would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis et al. to administer the peptide of SEQ ID NO:9 as a vaccine to a subject. One would have been motivated to do so given the suggestion by Klavinskis et al. that to prevent dissemination of HIV to the regional lymph nodes, an effective vaccine may need to stimulate CTL in the rectal or genital tract (see abstract and introduction), and the teachings of Ahlers et al. and Berzofsky et al. that SEQ ID NO:9 contains an immunodominant HIV CTL epitope. There would have been a reasonable expectation of success given the findings of Klavinskis et al. that mucosal or targeted lymph node immunization generates antigen-specific CTL in the rectal and genital

mucosa. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

Claims 1-16 and 25-37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-40 of U.S. Patent No. 6,749,856 (the '856 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because there is overlapping subject matter between the groups of claims. Specifically, the scope of the instant claims encompasses the scope of the '856 patent claims.

The patented claims are drawn to a method for inducing an antigen specific systemic and rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a rectal mucosal tissue of the subject with a composition comprising a chimeric peptide having the amino acid sequence KQIINMWQEVGKAMYAPPISGQIRIQRGPGRAFVTIGK (SEQ ID NO: 2). The instant claims are directed to a method for inducing a protective mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting a mucosal tissue of the subject with a composition comprising a purified soluble antigen. The methods are not patentably distinct.

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Tsuji et al., Enhancement of cell-mediated immunity against HIV-1 induced by coinoculation of plasmid-encoded HIV-1 antigen with plasmid expressing IL-12, The Journal of Immunology, 1997, 158:4008-4013. Tsuji et al. teaches enhanced CTL induction with IL-12 and DNA vaccines.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nicole E. Kinsey, Ph.D. whose telephone number is (571) 272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Nicole E Kinsey, Ph.D.
Examiner
Art Unit 1648

Stacy B. Chen 3/29/07

STACY B. CHEN
PRIMARY EXAMINER